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EXAMINER	
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/527,598	GAUDREAU, PIERRETTE	
	Examiner	Art Unit	
	Christina Marchetti Bradley	1654	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *24 March 2008*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *17-20,22-30,39 and 41-80* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *17-20,22-30,39 and 41-80* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Status of Claims

1. Claims 17-20, 22-30, 39 and 41-80 are pending. Claims 21, 31-35 and 40 were cancelled in the amendment filed 3/24/2008. All rejections of these claims are now moot. Claims 41-80 are newly added.

Claim Objections

2. The objection to claims 22-30 and 39 is withdrawn in light of the amendment filed 3/24/2008.

3. Claims 17-20, 22-30, 39 and 41-80 are objected to for the use of the acronym GHRH because it should be defined the first time it appears in the claims.

4. Claims 17-20 are objected to for the use of the transitional phrase "having". MPEP § 2105 states that the transitional phrases "having" must be interpreted in light of the specification to determine whether open or closed claim language is intended. The specification describes peptide consisting and comprising of the recited formula. Therefore, broadest reasonable interpretation of the transitional phrase "having" in claim 17 is open. However, the phrase is not explicitly defined in the specification and it is not readily apparent from the claim language what is intended. In order to clarify the scope of the claim, "having" should be changed to "consisting of" or "comprising".

5. Claims 17-20 and 48 are objected to for the following minor informality: the spacing in the formula of claims 17 and 48 is irregular. For example, sometimes there is a space in between the hyphen and the next amino acid (i.e. in claim 17 between Tyr- and D-Ala), sometimes there is not a space (i.e. in claim 17 Ala-Ile).

6. Claims 17-20, 22, 23, 25, 26, 28, 29, 39, 41-47, 49-52, 56-64, 68-71 and 80 are objected to. The claims define A30 as an amino acid sequence of 1 up to 15 residues. An amino acid sequence must include more than one amino acid. A30 should be defined as one amino acid or an amino acid sequence consisting of 2-15 residues.

7. Claims 23, 26, 29, 42 and 45 are objected to because of the format of the Markush Group. For example, in claim 23, A2 is D-Ala, A8 is Ala, A15 is Ala and A22 is Lys is not a GHRH analogue, it is merely a series of definitions. To clarify, claim 23 could be amended to

The pharmaceutical composition of claim 22, wherein

A2 is D-Ala, A8 is Ala, A15 is Ala and A22 is Lys;

A2 is D-Ala, A10 is D-Tyr, and A22 is Lys; or

A2 is D-Ala, A10 is D-Tyr, A15 is D-Ala, and A22 is Lys.

Alternatively, the options in the Markush Group should make reference to the formula of the parent claim.

8. Claims 22-30, 39 and 41-79 are objected to because "pharmaceutical acceptable salt" should be "pharmaceutically acceptable salt".

9. Claims 49 and 50 are objected to because "GIn" should be "Gln".

10. Claims 62 and 65 are objected to because "consists in a peptide" should be "consists of a peptide".

11. Claims 39, 47 and 80 are objected to for the use of "SEQ ID NO: 65". Claims 39, 47 and 80 each recite a formula and refer to it as SEQ ID NO: 65. In claims 39 and 80, A30 is defined as a bond or any amino acid sequence of 1 up to 15 residues, whereas in claim 47, A30 is defined as any amino acid sequence of 1 up to 15 residues. The sequence listing does not define A30 as

either a bond or any amino acid sequence of 1 up to 15 residues. Furthermore, in contrast with the formula in the claims, the sequence listing does not define the C-terminus of the peptide as an amide. Because of the D-amino acids in the formula, the amino acid sequence in claims 39, 47 and 80 is not required to have a sequence identifier. If Applicant chooses to use a sequence identifier for the formula, it should be used consistently throughout the claims and consistent with the sequence listing.

12. Claims 22-30 and 41-46 are objected to for the use of "SEQ ID NO: 67". Claims 22, 25, 28, 41 and 44 each recite a formula and refer to it as SEQ ID NO: 67. In claims 22, 25 and 28, A30 is defined as a bond or any amino acid sequence of 1 up to 15 residues, whereas in claims 41 and 44, A30 is defined as any amino acid sequence of 1 up to 15 residues. The sequence listing defines A30 as either a bond or any amino acid sequence of 1 up to 15 residues. Furthermore, in contrast with the formula in the claims, the sequence listing does not define the C-terminus of the peptide as an amide. Because of the D-amino acids in the formula, the amino acid sequence in claims 22, 25, 28, 41 and 44 is not required to have a sequence identifier. If Applicant chooses to use a sequence identifier for the formula, it should be used consistently throughout the claims and consistent with the sequence listing.

13. Claims 17-20 are objected to for the use of "SEQ ID NO: 66". Claim 17 recites a formula and refers to it as SEQ ID NO: 66. In contrast to the formula in the claim, the sequence listing does not define the C-terminus of the peptide as an amide. Because of the D-amino acids in the formula, the amino acid sequence in claim 17 is not required to have a sequence identifier. If Applicant chooses to use a sequence identifier for the formula, it should be used consistently throughout the claims and consistent with the sequence listing.

Claim Rejections - 35 USC § 112

14. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

15. Claims 22-24, 28-30 and 39 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. Claims 22, 28 and 39 have been amended to include the transitional phrase "consisting essentially of". The transitional phrase "consisting essentially of" is not explicitly supported in the specification as originally filed.

MPEP § 2105 states that the transitional phrase "consisting essentially of" limits the scope of a claim to the specified materials or steps "and those that do not materially affect the basic and novel characteristic(s)" of the claimed invention. In the instant case, claims 22, 28 and 39 are drawn to GNRH analogues consisting essentially of SEQ ID NOs: 67, 67 and 65, respectively. The scope of claims 22, 28 and 39 includes the GNRH analogue consisting of SEQ ID NOs: 67, 67 and 65, respectively. In addition, the scope of claims 22, 28 and 39 includes GNRH analogues consisting of SEQ ID NOs: 67, 67 and 65, respectively, and additional amino acids that do not materially affect the basic and novel characteristics of the peptide. The preamble of the claims limits the scope to analogues that are able to stimulate secretion or synthesis of growth hormone in a mammal. Thus, although not explicitly stated, the basic and novel characteristics of the peptides include this functional capability. However, the

specification does not explicitly or implicitly define the amino acid sequence which can be added to SEQ ID NO:s 65 or 67 without disrupting the ability to stimulate secretion or synthesis of growth hormone. The specification does not provide distinguishing characteristics including complete or partial structure, chemical or physical properties or a structure/function correlation for amino acids that can be added to SEQ ID NOs: 67 and 65 without materially affecting this basic and novel characteristic of the peptide. With the exception of GNRH analogues consisting of SEQ ID NOs: 65 and 67, one of ordinary skill in the art would not recognize that Applicant was in possession of GNRH analogues consisting essentially of SEQ ID NOs: 65 or 67 at the time of filing. Therefore, the newly added limitation "consisting essentially of" constitutes new matter.

Claim Rejections - 35 USC § 102

16. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

17. The rejection of claims 17-20 under 35 U.S.C. 102(b) as being anticipated by Gaudreau (U.S. Patent No. 5,854,216, cited reference A1 on the Information Disclosure Statement filed 2/7/2007) is withdrawn. Gaudreau does not teach the growth hormone releasing hormone (GHRH) analogue:

Tyr-D-Ala^{2}-Asp-Ala-Ile-Phe-Thr-Asn-Ser- D-Tyr^{10}-Arg-Lys-Val-Leu-D-Ala^{15}-Gln-Leu-Ser-Ala-Arg-Lys- Lys^{22}-Leu-Gln-Asp-Ile-Met-Ser-Arg-A30-NH_2

wherein A30 is an amino acid sequence of one up to fifteen residues.

18. The rejection of claims 22, 28 and 39 under 35 U.S.C. 102(b) as being anticipated by Gaudreau (U.S. Patent No. 5,854,216, cited reference A1 on the Information Disclosure Statement filed 2/7/2007) is maintained. In addition, claims 23, 29, 49, 50, 53 and 80 are rejected under 35 U.S.C. 102(b) as being anticipated by Gaudreau.

Gaudreau teaches methods of treating conditions such as burns by administering compounds comprising a fluorophore, linker and, individually, peptides consisting of the following GHRH analogues:

Tyr-D-Ala^{2}-Asp-Ala-Ile-Phe-Thr-Asn^{8}-Ser-D-Tyr^{10}-Arg-Lys-Val-Leu-Gly^{15}-Gln-Leu-Ser-Ala-Arg-Lys^{21}-Leu^{22}-Leu-Gln-Asp-Ile-Met-Ser-Arg-NH_2

wherein A2 is D-Ala, A8 is Asn, A9 is Ser, A10 is D-Tyr, A15 is Gly, A21 is Lys, A22 is Leu and A30 is a bond (claim 3, column 46, lines 4-7), which is a species of the peptide genus of claims 22, 25, 28, 39 and 80;

Tyr-D-Ala^{2}-Asp-Ala-Ile-Phe-Thr-Asn^{8}-Ser-D-Tyr^{10}-Arg-Lys-Val-Leu-D-Ala^{15}-Gln-Leu-Ser-Ala-Arg-Lys^{21}-Leu^{22}-Leu-Gln-Asp-Ile-Met-Ser-Arg-NH_2

wherein A2 is D-Ala, A8 is Asn, A9 is Ser, A10 is D-Tyr, A15 is D-Ala, A21 is Lys, A22 is Leu and A30 is a bond (claim 3, column 46, lines 8-11), which is a species of the peptide genus of claims 22, 25, 28, 39 and 80;

Tyr-Ala^{2}-Asp-Ala-Ile-Phe-Thr-D-Asn^{8}-Ser-Tyr^{10}-Arg-Lys-Val-Leu-Gly^{15}-Gln-Leu-Ser-Ala-Arg-Lys^{21}-Leu^{22}-Leu-Gln-Asp-Ile-Met-Ser-Arg-NH_2

wherein A2 is Ala, A8 is D-Asn, A9 is Ser, A10 is Tyr, A15 is Gly, A21 is Lys, A22 is Leu and A30 is a bond (claim 3, column 46, lines 36-39), which is a species of the peptide genus of claims 22, 25, 28, 39 and 80;

Tyr-Ala[2]-Asp-Ala-Ile-Phe-Thr-Ala[8]-Ser-Tyr[10]-Arg-Lys-Val-Leu-Ala[15]-Gln-Leu-Ser-Ala-Arg-Lys[21]-Ala[22]-Leu-Gln-Asp-Ile-Met-Ser-Arg-NH_2

wherein A2 is Ala, A8 is Ala, A9 is Ser, A10 is Tyr, A15 is Ala, A21 is Lys, A22 is Ala and A30 is a bond (claim 3, column 46, line 41), which is a species of the peptide genus of claims 22, 25, 28, 39 and 80;

Tyr-Ala[2]-Asp-Ala-Ile-Phe-Thr-Ala[8]-Ala[9]-Tyr[10]-Arg-Lys-Val-Leu-Ala[15]-Gln-Leu-Ser-Ala-Arg-Lys[21]-Ala[22]-Leu-Gln-Asp-Ile-Met-Ser-Arg-NH_2

wherein A2 is Ala, A8 is Ala, A9 is Ala, A10 is Tyr, A15 is Ala, A21 is Lys, A22 is Ala and A30 is a bond (claim 3, column 46, line 45), which is a species of the peptide genus of claims 22, 25, 28, 39 and 80;

Tyr-D-Ala[2]-Asp-Ala-Ile-Phe-Thr-Asn[8]-Ser-D-Tyr[10]-Arg-Lys-Val-Leu-Gly[15]-Gln-Leu-Ser-Ala-Arg-Lys[21]-Leu[22]-Leu-Gln-Asp-Ile-Met-Ser-Arg-NH_2

wherein A2 is D-Ala, A8 is Asn, A9 is Ser, A10 is D-Tyr, A15 is Gly, A21 is Lys, A22 is Leu and A30 is a bond (claim 3, column 46, line 13), which is a species of the peptide genus of claims 22, 25, 28, 39 and 80;

Tyr-D-Ala[2]-Asp-Ala-Ile-Phe-Thr-Asn[8]-Ser-D-Tyr[10]-Arg-Lys-Val-Leu-D-Ala[15]-Gln-Leu-Ser-Ala-Arg-Lys[21]-Leu[22]-Leu-Gln-Asp-Ile-Met-Ser-Arg-NH_2

wherein A2 is D-Ala, A8 is Asn, A9 is Ser, A10 is D-Tyr, A15 is D-Ala, A21 is Lys, A22 is Leu and A30 is a bond (claim 3, column 46, line 18), which is a species of the peptide genus of claims 22, 25, 28, 39 and 80;

Tyr-Ala[2]-Asp-Ala-Ile-Phe-Thr-Ala[8]-Ser-Tyr[10]-Arg-Lys-Val-Leu-Ala[15]-Gln-Leu-Ser-Ala-Arg-Lys[21]-Lys[22]-Leu-Gln-Asp-Ile-Met-Ser-Arg-NH_2

wherein A2 is Ala, A8 is Ala, A9 is Ser, A10 is Tyr, A15 is Ala, A21 is Lys, A22 is Lys and A30 is a bond (claim 3, column 46, line 23), which is a species of the peptide genus of claims 22, 25, 28, 39 and 80; and

Tyr-D-Ala^{2}-Asp-Ala-Ile-Phe-Thr-Ala^{8}-Ser-Tyr^{10}-Arg-Lys-Val-Leu-Ala^{15}-Gln-Leu-Ser-Ala-Arg-Lys^{21}-Lys^{22}-Leu-Gln-Asp-Ile-Met-Ser-Arg-NH_2

wherein A2 is D-Ala, A8 is Ala, A9 is Ser, A10 is Tyr, A15 is Ala, A21 is Lys, A22 is Lys and A30 is a bond (claim 3, column 46, line 60), which is a species of the peptide genus of claims 22, 23, 28, 29, 39, 49, 50, 53, and 80.

In order to treat conditions such as burns, these compounds must be combined with a pharmaceutically acceptable carrier. That is, in order to topically administer a peptide-based drug, the drug must be combined with a gel or cream, for example. Therefore, the limitation that the composition include a pharmaceutically acceptable carrier is implicit in the teaching of Gaudreau.

Gaudreau does not teach that the GHRH analogues can stimulate secretion or synthesis of growth hormone in a mammal. Because the chemical structures of the species taught by Gaudreau are identical to the claimed invention, the species must meet this functional limitation. If the composition is physically the same, it must have the same functional properties. "Products of identical chemical composition can not have mutually exclusive properties." A chemical composition and its properties are inseparable. Therefore, if the prior art teaches the identical chemical structure, the properties applicant discloses and/or claims are necessarily present. *In re Spada*, 911 F.2d 705, 709, 15 USPQ2d 1655, 1658 (Fed. Cir. 1990) See MPEP § 2112.01.

In the response filed 3/24/2008, Applicant traverses the rejection of claims 22, 28 and 39 stating that the claims have been amended to include the limitation "said GHRH analogue or salt consisting essentially of the formula: Tyr-…-A30-NH2". The prior art reference of Gaudreau meets this newly added limitation because the compounds taught by Gaudreau must exhibit biological activity equivalent to GRF (col. 4, lines 59-67). Therefore, the linker and fluorophore which are included in the compounds taught by Gaudreau in addition to the instantly claimed peptide formulas do not materially affect the basic and novel characteristics of the compound. In addition, MPEP § 2105 states that for the purposes of searching for and applying prior art under 35 U.S.C. 102 and 103, absent a clear indication in the specification or claims of what the basic and novel characteristics actually are, "consisting essentially of" will be construed as equivalent to "comprising." As argued above, the specification does not a provide a clear indication of materials that can be added to the recited peptide formulas without materially affecting their basic and novel characteristics. The compounds of Gaudreau, which comprise the claimed peptide sequences, meet the structural limitations of the claim.

In addition, in the response filed 3/24/2008, Applicant traverses the rejection arguing that Gaudreau is "silent with regard to a GHRH analogues and formulations having the combination of features set forth in amended claims 22, 28 and 39." This argument is not persuasive. As stated above, Gaudreau teaches all the limitations of claims 22, 28 and 29.

19. Claims 22, 25, 28, 39 and 80 are rejected under 35 U.S.C. 102(b) as being anticipated by Coy *et al.* (*J. Med. Chem.*, **1985**, *28*, 181-5). Coy *et al.* teach [15-D-alanine-29-L-argininamide]-GRF(1-29). With respect to the formula in claims 22, 25, 28, 39 and 80, A2 is Ala, A8 is Asn,

A9 is Ser, A10 is Tyr, A15 is D-Ala, A21 is Lys, A22 is Leu and A30 is a bond (Figure 1, Table 1, number 9). Coy *et al.* teach that the GRF analogue stimulates growth hormone in rat when administered in a pharmaceutical composition also comprising saline as the carrier (Table 1).

20. Claims 22, 25, 28, 39 and 80 are rejected under 35 U.S.C. 102(b) as being anticipated by Lefrancois *et al.* (*Neuroendocrinology*, **1994**, *59*, 363-70). Lefrancois *et al.* teach the GNRH analogues: [2-D-Ala]hGRF(1-29)NH_2, [8-D-Asn]hGRF(1-29)NH_2, [10-D-Tyr]hGRF(1-29)NH_2, [21-D-Lys]hGRF(1-29)NH_2, [22-D-Leu]hGRF(1-29)NH_2, [8-Ala]hGRF(1-29)NH_2, [9-Ala]hGRF(1-29)NH_2, [15-Ala]hGRF(1-29)NH_2, and [22-Ala]hGRF(1-29)NH_2 (abstract). The analogues were included in compositions for pituitary cell culture assays that also included the pharmaceutically acceptable carrier water. Lefrancois *et al.* do not teach that the GHRH analogues can stimulate secretion or synthesis of growth hormone in a mammal. Because the chemical structures of the species taught by Lefrancois *et al.* are identical to the claimed invention, the species must meet this functional limitation. If the composition is physically the same, it must have the same functional properties. "Products of identical chemical composition can not have mutually exclusive properties." A chemical composition and its properties are inseparable. Therefore, if the prior art teaches the identical chemical structure, the properties applicant discloses and/or claims are necessarily present. *In re Spada*, 911 F.2d 705, 709, 15 USPQ2d 1655, 1658 (Fed. Cir. 1990) See MPEP § 2112.01.

21. Claims 22, 25, 28, 39, 41, 44, 47 and 80 are rejected under 35 U.S.C. 102(b) as being anticipated by Campbell *et al.* (*J. Pept. Res.*, **1997**, *49*, 527-37). Campbell *et al.* teach the

GHRH analogue [Ala^{15}]hGRF(1-29)[Gly^{30}-Gly^{31}-Cys^{32}]NH_2 wherein the Cys^{32} is monopegylated (abstract) in a composition suitable for *in vitro* and *in vivo* biological assay. In this analogue, A30 is three amino acids long. Campbell *et al.* teach that the analogue retains its growth hormone stimulating activity (abstract).

Claim Rejections - 35 USC § 103

22. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

23. The rejection of claims 17-20, 22-30 and 39 under 35 U.S.C. 103(a) as being unpatentable over Gaudreau (U.S. Patent No. 5,854,216, cited reference A1 on the Information Disclosure Statement filed 2/7/2007) is maintained. In addition, claims 41-80 are rejected under 35 U.S.C. 103(a) as being unpatentable over Gaudreau.

Gaudreau teaches pharmaceutical compositions comprising compounds of the formula Ra-X-Rb wherein Rb represents GHRH analogue peptides covalently linked to a fluorophore (Ra) via a linker (X), and a pharmaceutically acceptable carrier suitable to treat conditions such as hypothalamic pituitary dwarfism, burns, osteoporosis, renal failure, non-union-bone fracture, wounds, post-surgical problems, lactation failure, female infertility, cachexia, T-cell immunodeficiencies, neurodegenerative conditions and GRF receptor-dependent tumors (claim 3).

The compounds taught by Gaudreau include peptides consisting of the following GHRH analogues:

Tyr-D-Ala^{2}-Asp-Ala-Ile-Phe-Thr-Asn^{8}-Ser-D-Tyr^{10}-Arg-Lys-Val-Leu-Gly^{15}-Gln-Leu-Ser-Ala-Arg-Lys^{21}-Leu^{22}-Leu-Gln-Asp-Ile-Met-Ser-Arg-NH_2

wherein A2 is D-Ala, A8 is Asn, A9 is Ser, A10 is D-Tyr, A15 is Gly, A21 is Lys, A22 is Leu and A30 is a bond (claim 3, column 46, lines 4-7; Tables 10 and 11, compound 2), which is a species of the peptide genus of claims 22, 25, 28, 39 and 80;

Tyr-D-Ala^{2}-Asp-Ala-Ile-Phe-Thr-Asn^{8}-Ser-D-Tyr^{10}-Arg-Lys-Val-Leu-D-Ala^{15}-Gln-Leu-Ser-Ala-Arg-Lys^{21}-Leu^{22}-Leu-Gln-Asp-Ile-Met-Ser-Arg-NH_2

wherein A2 is D-Ala, A8 is Asn, A9 is Ser, A10 is D-Tyr, A15 is D-Ala, A21 is Lys, A22 is Leu and A30 is a bond (claim 3, column 46, lines 8-11; Tables 10 and 11, compound 3), which is a species of the peptide genus of claims 22, 25, 28, 39 and 80;

Tyr-Ala^{2}-Asp-Ala-Ile-Phe-Thr-D-Asn^{8}-Ser-Tyr^{10}-Arg-Lys-Val-Leu-Gly^{15}-Gln-Leu-Ser-Ala-Arg-Lys^{21}-Leu^{22}-Leu-Gln-Asp-Ile-Met-Ser-Arg-NH_2

wherein A2 is Ala, A8 is D-Asn, A9 is Ser, A10 is Tyr, A15 is Gly, A21 is Lys, A22 is Leu and A30 is a bond (claim 3, column 46, lines 36-39), which is a species of the peptide genus of claims 22, 25, 28, 39 and 80;

Tyr-Ala^{2}-Asp-Ala-Ile-Phe-Thr-Ala^{8}-Ser-Tyr^{10}-Arg-Lys-Val-Leu-Ala^{15}-Gln-Leu-Ser-Ala-Arg-Lys^{21}-Ala^{22}-Leu-Gln-Asp-Ile-Met-Ser-Arg-NH_2

wherein A2 is Ala, A8 is Ala, A9 is Ser, A10 is Tyr, A15 is Ala, A21 is Lys, A22 is Ala and A30 is a bond (claim 3, column 46, line 41; Tables 10 and 11, compound 10), which is a species of the peptide genus of claims 22, 25, 28, 39 and 80;

Tyr-Ala^{2}-Asp-Ala-Ile-Phe-Thr-Ala^{8}-Ala^{9}-Tyr^{10}-Arg-Lys-Val-Leu-Ala^{15}-Gln-Leu-Ser-Ala-Arg-Lys^{21}-Ala^{22}-Leu-Gln-Asp-Ile-Met-Ser-Arg-NH_2

wherein A2 is Ala, A8 is Ala, A9 is Ala, A10 is Tyr, A15 is Ala, A21 is Lys, A22 is Ala and A30 is a bond (claim 3, column 46, line 45; Tables 10 and 11, compound 11), which is a species of the peptide genus of claims 22, 25, 28, 39 and 80;

Tyr-D-Ala^{2}-Asp-Ala-Ile-Phe-Thr-Asn^{8}-Ser-D-Tyr^{10}-Arg-Lys-Val-Leu-Gly^{15}-Gln-Leu-Ser-Ala-Arg-Lys^{21}-Leu^{22}-Leu-Gln-Asp-Ile-Met-Ser-Arg-NH_2

wherein A2 is D-Ala, A8 is Asn, A9 is Ser, A10 is D-Tyr, A15 is Gly, A21 is Lys, A22 is Leu and A30 is a bond (claim 3, column 46, line 13), which is a species of the peptide genus of claims 22, 25, 28, 39 and 80;

Tyr-D-Ala^{2}-Asp-Ala-Ile-Phe-Thr-Asn^{8}-Ser-D-Tyr^{10}-Arg-Lys-Val-Leu-D-Ala^{15}-Gln-Leu-Ser-Ala-Arg-Lys^{21}-Leu^{22}-Leu-Gln-Asp-Ile-Met-Ser-Arg-NH_2

wherein A2 is D-Ala, A8 is Asn, A9 is Ser, A10 is D-Tyr, A15 is D-Ala, A21 is Lys, A22 is Leu and A30 is a bond (claim 3, column 46, line 18), which is a species of the peptide genus of claims 22, 25, 28, 39 and 80;

Tyr-Ala^{2}-Asp-Ala-Ile-Phe-Thr-Ala^{8}-Ser-Tyr^{10}-Arg-Lys-Val-Leu-Ala^{15}-Gln-Leu-Ser-Ala-Arg-Lys^{21}-Lys^{22}-Leu-Gln-Asp-Ile-Met-Ser-Arg-NH_2

wherein A2 is Ala, A8 is Ala, A9 is Ser, A10 is Tyr, A15 is Ala, A21 is Lys, A22 is Lys and A30 is a bond (claim 3, column 46, line 23), which is a species of the peptide genus of claims 22, 25, 28, 39 and 80; and

Tyr-D-Ala^{2}-Asp-Ala-Ile-Phe-Thr-Ala^{8}-Ser-Tyr^{10}-Arg-Lys-Val-Leu-Ala^{15}-Gln-Leu-Ser-Ala-Arg-Lys^{21}-Lys^{22}-Leu-Gln-Asp-Ile-Met-Ser-Arg-NH_2

wherein A2 is D-Ala, A8 is Ala, A9 is Ser, A10 is Tyr, A15 is Ala, A21 is Lys, A22 is Lys and A30 is a bond (claim 3, column 46, line 60; Tables 10 and 11, compound 13), which is a species of the peptide genus of claims 22, 23, 25, 26, 28, 29, 39, 49, 50, 53, 62, 65 and 80.

Gaudreau does not teach a pharmaceutical composition comprising the aforementioned GNRH analogues in the absence of conjugation to Ra-X-.

It would have been obvious to make GHRH analogues consisting of the aforementioned peptides in the absence of conjugation to Ra-X- and to dissolve them in a pharmaceutically-acceptable carrier such as water. The skilled artisan would have been motivated to do so based on the teaching of Gaudreau that the peptides possess biological activity, a binding affinity to the receptor in rat adenopituitary cells equivalent to or greater than that of wild type hGRF(1-29)NH_2 (Table 11), and can be used to treat a variety of conditions such as hypothalamic pituitary dwarfism, burns, osteoporosis, renal failure, non-union-bone fracture, wounds, post-surgical problems, lactation failure, female infertility, cachexia, T-cell immunodeficiencies, neurodegenerative conditions and GRF receptor-dependent tumors (claim 3). The skilled artisan would have been motivated to use the peptides in the absence of Ra-X- because it is the peptide, not the conjugated fluorophore, that possesses the relevant biological activity. The skilled artisan would have been further motivated to combine the peptide with a pharmaceutically acceptable carrier suitable for the specific condition to be treated and the desired mode of administration (i.e. topical for the treatment of burns and subcutaneous injection, intravenous or oral osteoporosis, for example). There would have been a reasonable expectation of success given that the GHRH analogue peptides can be synthesized using solid state methods and mixed in water or another pharmaceutically acceptable carrier.

Gaudreau also teaches the GHRH analogues consisting of:

Tyr-D-Ala^{2}-Asp-Ala-Ile-Phe-Thr-Asn-Ser- D-Tyr^{10}-Arg-Lys-Val-Leu-D-Ala^{15}-Gln-Leu-Ser-Ala-Arg-Lys^{21}-Lys^{22}-Leu-Gln-Asp-Ile-Met-Ser-Arg-NH_2

wherein A2 is D-Ala, A8 is Asn, A10 is D-Tyr, A15 is D-Ala, A21 is Lys, A22 is Lys and A30 is a bond (Tables 10 and 11, compound 8), which is identical to the peptide species recited in claims 21, 24, 27 and 30, and is a species within the peptide genus recited in claims 22- 30, 39, 48-50, 52, 53, 55, 62, 64, 65, 67 and 80;

Tyr-D-Ala^{2}-Asp-Ala-Ile-Phe-Thr-Asn-Ser-D-Tyr^{10}-Arg-Lys-Val-Leu-Gly^{15}-Gln-Leu-Ser-Ala-Arg-D-Lys^{21}-Leu^{22}-Leu-Gln-Asp-Ile-Met-Ser-Arg-NH_2

wherein A2 is D-Ala, A8 is Asn, A9 is Ser, A10 is D-Tyr, A15 is Gly, A21 is D-Lys, A22 is Leu and A30 is a bond (Tables 10 and 11, compound 4), which is a species within the peptide genus recited in claims 22, 25, 28, 39 and 80;

Tyr-D-Ala^{2}-Asp-Ala-Ile-Phe-Thr-Asn-Ser-D-Tyr^{10}-Arg-Lys-Val-Leu-D-Ala^{15}-Gln-Leu-Ser-Ala-Arg-D-Lys^{21}-Leu^{22}-Leu-Gln-Asp-Ile-Met-Ser-Arg-NH_2

wherein A2 is D-Ala, A8 is Asn, A9 is Ser, A10 is D-Tyr, A15 is D-Ala, A21 is D-Lys, A22 is Leu and A30 is a bond (Tables 10 and 11, compound 5), which is a species within the peptide genus recited in claims 22, 25, 28, 39 and 80;

Tyr-Ala^{2}-Asp-Ala-Ile-Phe-Thr-Ala-Ser-Tyr^{10}-Arg-Lys-Val-Leu-Gly^{15}-Gln-Leu-Ser-Ala-Arg-Lys^{21}-Lys^{22}-Leu-Gln-Asp-Ile-Met-Ser-Arg-NH_2

wherein A2 is Ala, A8 is Ala, A9 is Ser, A10 is Tyr, A15 is Gly, A21 is Lys, A22 is Lys and A30 is a bond (Tables 10 and 11, compound 6), which is a species within the peptide genus recited in claims 22, 25, 28, 39 and 80;

Tyr-D-Ala^{2}-Asp-Ala-Ile-Phe-Thr-Asn-Ser-D-Tyr^{10}-Arg-Lys-Val-Leu-Gly^{15}-Gln-Leu-Ser-Ala-Arg-Lys^{21}-Lys^{22}-Leu-Gln-Asp-Ile-Met-Ser-Arg-NH_2

wherein A2 is D-Ala, A8 is Asn, A9 is Ser, A10 is D-Tyr, A15 is Gly, A21 is Lys, A22 is Lys and A30 is a bond (Tables 10 and 11, compound 7), which is a species within the peptide genus recited in claims 22, 23, 25, 26, 28, 29, 39, 49-51, 53, 54, 62, 63, 65, 66 and 80;

Tyr-Ala^{2}-Asp-Ala-Ile-Phe-Thr-D-Asn-Ser-Tyr^{10}-Arg-Lys-Val-Leu-Gly^{15}-Gln-Leu-Ser-Ala-Arg-Lys^{21}-D-Leu^{22}-Leu-Gln-Asp-Ile-Met-Ser-Arg-NH_2

wherein A2 is Ala, A8 is D-Asn, A9 is Ser, A10 is Tyr, A15 is Gly, A21 is Lys, A22 is D-Leu and A30 is a bond (Tables 10 and 11, compound 9), which is a species within the peptide genus recited in claims 22, 25, 28, 39 and 80; and

Tyr-D-Ala^{2}-Asp-Ala-Ile-Phe-Thr-Ala-Ser-D-Tyr^{10}-Arg-Lys-Val-Leu-Ala^{15}-Gln-Leu-Ser-Ala-Arg-D-Lys^{21}-Lys^{22}-Leu-Gln-Asp-Ile-Met-Ser-Arg-NH_2

wherein A2 is D-Ala, A8 is Ala, A9 is Ser, A10 is D-Tyr, A15 is Ala, A21 is D-Lys, A22 is Lys and A30 is a bond (Tables 10 and 11, compound 14), which is a species within the peptide genus recited in claims 22, 23, 25, 26, 28, 29, 39 and 80.

It would have been obvious to make GHRH analogues consisting of the aforementioned peptides and to dissolve them in a pharmaceutically-acceptable carrier such as water. The skilled artisan would have been motivated to do so based on the teaching of Gaudreau that the peptides possess biological activity, a binding affinity to the receptor in rat adenopituitary cells equivalent to or greater than that of wild type hGRF(1-29)NH_2 (Table 11), and that related peptides can be used to treat a variety of conditions such as hypothalamic pituitary dwarfism, burns, osteoporosis, renal failure, non-union-bone fracture, wounds, post-surgical problems, lactation

failure, female infertility, cachexia, T-cell immunodeficiencies, neurodegenerative conditions and GRF receptor-dependent tumors (claim 3). The skilled artisan would have been motivated to use the peptides in the absence of Ra-X- because it is the peptide, not the conjugated fluorophore, that possesses the relevant biological activity. The skilled artisan would have been further motivated to combine the peptide with a pharmaceutically acceptable carrier suitable for the specific condition to be treated and the desired mode of administration (i.e. topical for the treatment of burns and subcutaneous injection, intravenous or oral osteoporosis, for example). There would have been a reasonable expectation of success given that the GHRH analogue peptides can be synthesized using solid state methods and mixed in water or another pharmaceutically acceptable carrier.

With respect to claims 41-47, it would have been obvious to make the amino acid substitutions present in the GHRH analogues recited above in the full-length GHRH which consists of 44 residues. In these variants, A30 would equal an amino acid sequence of 15 residues, satisfying the structural limitations of claims 17-20 and 41-47. The skilled artisan would have been motivated to do so based on the teaching that the full-length and the 1-29 analogue have the same biological properties, and that therefore, substitutions that increase binding affinity to the GRF receptor in the truncated form could likewise have an effect on the binding affinity of the full-length peptide. The skilled artisan would have been further motivated to dissolve the peptides in a pharmaceutically acceptable carrier such as water. There would have been a reasonable expectation of success because methods of peptide synthesis are well-known in the art.

With respect to claims 56-62 and 68-79, it would have been obvious to optimize the dosage of the GNRH peptides through routine experimentation. MPEP § 2144.05 states that generally, differences in concentration or temperature will not support the patentability of subject matter encompassed by the prior art unless there is evidence indicating such concentration or temperature is critical. In the instant case, there is no evidence that the claimed ranges of 0.001 mg/ml to 3 mg/ml or 0.001 mg/kg body weight to 3 mg/kg body weight, which span three orders of magnitude, are nonobvious over the prior art of Gaudreau or that they could not be arrived at through routine experimentation. Furthermore, the dose in the composition depends on the mode of delivery and the condition being treated, which are not specified in the instant claims.

24. In the response filed 3/24/2008, Applicant traverses the rejection on three grounds: 1) that the Gaudreau reference is silent on the use of GRF analogues lacking the Ra-X- portion of the subject compounds; 2) that there is no motivation to select the [D-Ala^2, D-Tyr^{10}, D-Ala^{15}, Lys^{22}]hGRF(1-29)NH_2 analogue from all of the recited analogues; and 3) that the Gaudreau reference does not teach that the [D-Ala^2, D-Tyr^{10}, D-Ala^{15}, Lys^{22}]hGRF(1-29)NH_2 analogue is capable of stimulating the synthesis or secretion of growth hormone in a mammal or that the the [D-Ala^2, D-Tyr^{10}, D-Ala^{15}, Lys^{22}]hGRF(1-29)NH_2 analogue binds to the human GHRH receptor with greater than 9000x affinity. These arguments are not persuasive. As discussed above, it would have been obvious to make all of the peptide recited in claim 3 and in Tables 10 and 11 of Gaudreau without the Ra-X- portion of the compounds. Gaudreau makes these peptides and tests their affinity for the GRF receptor in the absence of the fluorophore (Table 11). Given that the biological activity of the compounds of Gaudreau is attributed to the peptide portion, Rb, and not to the fluorophore/linker portion, Ra-X-, the skilled artisan would have been motivated to

make the peptides in the absence of these additional moieties. In addition, rather than select the [D-Ala^2, D-Tyr^{10}, D-Ala^{15}, Lys^{22}]hGRF(1-29)NH_2 analogue exclusively, the skilled artisan would have been motivated to make all of the peptides recited in Gaudreau. Given that the analogues exhibit equivalent or greater affinity to the GRF receptor and can be used to treat a variety of conditions, the skilled artisan would have been motivated to make them, dissolve them in a pharmaceutically acceptable carrier and use them to identify effective treatments for conditions such as hypothalamic pituitary dwarfism, burns, osteoporosis, renal failure, non-union-bone fracture, wounds, post-surgical problems, lactation failure, female infertility, cachexia, T-cell immunodeficiencies, neurodegenerative conditions and GRF receptor-dependent tumors. Finally, Gaudreau does not teach that the GHRH analogues have an *in vitro* potency index substantially higher than the *in vitro* potency index of a native hGHRH(1-29), that the GHRH analogues can stimulate secretion or synthesis of growth hormone in a mammal or that the [D-Ala^2, D-Tyr^{10}, D-Ala^{15}, Lys^{22}]hGRF(1-29)NH_2 has a greater than 9000x affinity for the GRF receptor. Because the chemical structures of the species taught by Gaudreau are identical to the claimed invention, the species must meet this functional limitation. If the composition is physically the same, it must have the same functional properties. "Products of identical chemical composition can not have mutually exclusive properties." A chemical composition and its properties are inseparable. Therefore, if the prior art teaches the identical chemical structure, the properties applicant discloses and/or claims are necessarily present. *In re Spada*, 911 F.2d 705, 709, 15 USPQ2d 1655, 1658 (Fed. Cir. 1990) See MPEP § 2112.01. There would have been a reasonable expectation that these peptides would meet these functional limitations in light of the

fact that Gaudreau claims them for pharmaceutical use to treat a variety of conditions and that the peptides exhibit binding affinity for the rat GRF receptor.

For these reasons, the rejection is maintained.

Conclusion

25. No claims are allowed.
26. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Christina Marchetti Bradley whose telephone number is (571) 272-9044. The examiner can normally be reached on Monday, Tuesday, Thursday and Friday, 9:00 A.M. to 3:30 P.M.
27. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Cecilia Tsang can be reached on (571) 272-0562. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.
28. Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

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